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Antifungal prophylaxis in haematology patients: the role of voriconazole

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Abstract

Invasive fungal infections (IFIs) are a major cause of morbidity and mortality in haematopoietic stem cell transplant (HCT) recipients and patients with haematological malignancies. Early treatment initiation is vital for improving survival, but is hampered by difficulties in timely diagnosis. Prophylaxis with a broad-spectrum antifungal, such as voriconazole, has the potential to decrease the incidence of IFI in haematology patients. Based on a growing body of data, voriconazole appears to be effective for the primary and secondary prevention of IFIs in HCT recipients, with generally good tolerability.

Keywords: Antifungal prophylaxis, haematology, leukaemia, stem cell transplantation, voriconazole

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Introduction

Invasive fungal infections (IFIs) are a significant cause of morbidity and mortality in haematology patients. Haematopoietic stem cell transplant (HCT) recipients and patients with haematological malignancies are particularly vulnerable, as a consequence of their underlying condition, its treatment, or prolonged immunosuppression [1–6]. Invasive aspergillosis (IA) is the most important IFI in these populations and is the leading cause of infection-related death in HCT recipients [7]. The onset of invasive *Aspergillus* infection following HCT appears to be bimodal, occurring more frequently during the graft-versus-host disease (GvHD) period late after engraftment [3,8,9]. Patients undergoing autologous HCT rarely present with IA and have a distinctly lower attributable mortality rate than allograft recipients [10]. Besides IA, other invasive mould infections and invasive candidiasis are also fairly common [3,6,8,11,12]. Recent data show that about three-quarters of IFIs in HCT patients are caused by moulds, mostly in the form of IA (59–71%), with the remainder caused by *Candida* spp. [10,13,14]. Furthermore, invasive mould infections, especially those caused by *Aspergillus*, appear to be becoming increasingly frequent in various haematology populations [3,4,8].

These trends are probably linked to the growing number of at-risk patients (e.g. elderly patients undergoing reduced-intensity conditioning HCT, solid organ transplant recipients, and critically ill patients) as well as the increasing prevalence of risk factors rendering patients susceptible to IFIs in general and invasive mould infections in particular. Such risk factors include cytotoxic chemotherapy, neutropenia, GvHD, immunosuppressant therapy, broad-spectrum antibiotics, use of intravenous catheters, parenteral nutrition and renal failure [1,3]. In haematology patients, the risk for developing an IFI depends strongly on the severity and duration of myelosuppression and immunosuppression [15]. The overall developments in epidemiology are of concern because IFIs are associated with substantial mortality. In Europe, mortality rates range from 27 to 94% for IA and from 28 to 59% for invasive candidiasis [10,16–24].

Although early initiation of therapy is vital for improving treatment outcomes, the timely diagnosis and treatment of IFIs pose considerable challenges [3,25,26]. Given the lack of validated early treatment strategies, mould-active prophylaxis

may currently be the most attractive option for the management of IFIs in specific groups of haematology patients, until tests for the early detection of IFI have become more reliable [26–30]. This preventative approach has the potential of decreasing IFI incidence and concurrently improving survival in haematology patients; however, data from recent clinical trials suggest that it does not entirely avoid the need for additional empirical or pre-emptive therapy [31–34].

There are also some concerns about the widespread application of antifungal prophylaxis, such as induction of antimicrobial resistance, shifts in epidemiology, avoidable drug toxicity and costs, and considerable variability in the plasma levels of certain antifungals [15,27,35]. This review will address current issues in antifungal prophylaxis for HCT recipients and haematological malignancy patients, with a particular focus on recent data supporting the potential value of voriconazole in this setting.

Antifungal prophylaxis

The use of any chemoprophylaxis in medicine ought to be supported by a number of key tenets. For instance, the disease to be prevented should be associated with a high mortality rate, and the preventative agent should have an acceptable efficacy and safety profile. Furthermore, optimum IFI prophylaxis requires the selection of patients at highest risk of invasive fungal disease, to limit drug exposure to those individuals who are most likely to benefit from this strategy [36,37]. Novel approaches toward the identification of high-risk patients have shown the importance of host innate immunity, with several genetic polymorphisms (i.e. of *TLR4*, *IL10*, *DECTIN*-1, and the plasminogen gene) having potential as specific risk markers [35,38]. Some authors propose to restrict prophylaxis with broad-spectrum azoles to those institutions that have a relatively high incidence of invasive mould infections or that do not routinely employ effective strategies for early diagnosis and treatment [36,39]. However, so far there is no consensus on how to define populations of haematology patients that are at 'high-risk for IFI' on the basis of a minimum IFI incidence rate or a minimum number needed-to-treat, and in whom primary antifungal prophylaxis may therefore be preferable to other management approaches. Besides chemoprophylaxis, protective isolation in conjunction with the use of high-efficiency particulate air filtration systems may also be useful for the prevention of systemic mould infections in patients undergoing allogeneic HCT or chemotherapy for acute leukaemia [1,36].

The optimal duration of antifungal prophylaxis in haematology patients also remains to be confirmed. In HCT recipients, prophylactic therapy may need to be administered for a minimum of 6 months following transplant [15], in particular when considering the increasing frequency of late-onset IA [8,26]. The efficacy of antifungal prophylaxis during this time may partially depend on the degree of immunosuppression, as indicated by biological markers (e.g. levels of CD4 T lymphocytes) [15]. Also still unknown are the most effective agents for antifungal prophylaxis in HCT recipients or patients receiving chemotherapy for haematological disease (Table 1) [31,32,34,40–48], even though mould-active azoles seem to have the most potential in these settings. Among that class of agents, the second-generation, broad-spectrum triazole voriconazole is emerging as a new option for primary and secondary antifungal prophylaxis.

The potential of voriconazole as antifungal prophylaxis

Voriconazole is currently indicated for the treatment of invasive aspergillosis, candidaemia in non-neutropenic patients, and serious infections caused by *Scedosporium* and *Fusarium* spp. Furthermore, in Europe the agent is licensed for the treatment of fluconazole-resistant serious invasive *Candida* infections and in the USA for oesophageal candidiasis and disseminated *Candida* infections in skin, abdomen, kidney, bladder wall and wounds [49,50]. This variety of indications is reflected by the broad *in vitro* spectrum of voriconazole against yeasts and moulds, including *Aspergillus* spp., *Candida* spp., *Fusarium* spp., *Scedosporium apiospermum*, dematiaceous moulds, *Cryptococcus neoformans* and dimorphic fungi. Of note, voriconazole is not active against the zygomycetes and may have reduced activity against certain strains of *Candida glabrata* and *Candida albicans* that have acquired fluconazole resistance [51].

The extended spectrum of voriconazole gives it potential value as a prophylactic agent. The *in vitro* coverage and documented clinical efficacy of voriconazole against the majority of fungal pathogens [20,51–55] may make it particularly useful for the prevention of IFIs in the haematology setting, where invasive mould infections play a prominent role. Of note, voriconazole is now generally recommended as first-line treatment for proven or probable IA [56–60], the most significant systemic fungal disease affecting haematology populations; a recent mixed-treatment comparison suggested that voriconazole may be the most effective antifungal for improving patient survival in the setting of directed therapy [61]. On the other hand, the very fact that voriconazole is widely considered the standard treatment for documented IA may pose an issue when using mould-active azoles prophylactically in the same patient population, because of the risk of selection

TABLE 1. Summary of different options for the prophylaxis of invasive fungal infections in haematology patients, based on results from clinical trials published since 2000

Antifungal agent	*In vitro* activity, MIC_{90} (mg/L) [43]	Clinical prophylaxis trials	Advantages and disadvantages	Recommendation from international guidelines[a]
Voriconazole	All fungi: 0.5	600 allo-HCT patients [34]; voriconazole vs. fluconazole for 100 or 180 days (in higher-risk patients); IFI incidence: voriconazole, 7.3% vs. fluconazole, 11.2% (ns); FFS at 180 days: voriconazole, 75% vs. fluconazole, 78% (ns); OS also similar	Potent *in vitro* activity against broad range of clinically important fungal pathogens [43]	IDSA: (no comment on voriconazole)
	All moulds: 2.0	489 allo-HCT patients [32]; voriconazole vs. itraconazole for ≤180 days; prophylactic success: voriconazole, 49% vs. itraconazole, 33% (p <0.01); tolerated treatment for ≥100 days (with ≤14 days interruption): voriconazole, 54% vs. itraconazole, 39% (p <0.01); incidence of proven/probable IFI: voriconazole, 1.3% vs. itraconazole, 2.1% (ns); survival to day 180: voriconazole, 82% vs. itraconazole, 81% (ns)	Effective in treatment of aspergillosis in severely immunocompromised patients [48]	ECIL-3: Provisional AI in allo-HCT during initial neutropenic phase and GvHD phase
	All yeasts: 0.5		No activity against zygomycetes [45] Complicated pharmacokinetics, important drug interactions, and relatively significant AEs [48]	
Posaconazole	All fungi: 1.0	600 patients with severe GvHD [46]; posaconazole vs. fluconazole for 112 days; overall IFI incidence: posaconazole, 5.3% vs. fluconazole, 9.0% (ns); proven/probable IA: posaconazole, 2.3% vs. fluconazole, 7.0% (p 0.006); Number of deaths: posaconazole, 1% vs. fluconazole, 4% (p 0.046)	Extended antifungal spectrum, including significant activity against zygomycetes [43,48,45]; good safety profile [48]	IDSA (IA prophylaxis): AI in neutropenic patients with AML/MDS and allo-HCT recipients with GvHD
	All moulds: 1.0	602 patients with prolonged neutropenia due to chemotherapy for AML or MDS [31]; posaconazole vs. fluconazole or itraconazole for 100 days; overall IFI incidence: posaconazole, 5% vs. fluconazole or itraconazole, 11% (p 0.003); proven/probable IA: posaconazole, 1% vs. fluconazole or itraconazole, 7% (p <0.001); Overall mortality: posaconazole, 16% vs. fluconazole or itraconazole, 22% (p 0.04)	Requires multiple daily dosing and fatty foods for absorption; in the absence of intravenous formulation, restricting its use to select patients [48]	IDSA (IC prophylaxis): AI in patients with chemotherapy-induced neutropenia and stem cell transplant recipients with neutropenia
	All yeasts: 1.0			ECIL-3: AI in leukaemia induction chemotherapy and allo-HCT recipients during GvHD phase
Itraconazole	All fungi: 1.0	304 allo-HCT patients [40]; itraconazole vs. fluconazole for 180 days; overall IFI incidence: itraconazole, 13% vs. fluconazole, 16% (ns); IFI incidence on treatment: itraconazole, 7% vs. fluconazole, 15% (p 0.03); OS (ns); FFS (ns)	Significant activity against *Aspergillus* spp. [48]	IDSA (IA prophylaxis): BI
	All moulds: 4.0	140 allo-HCT patients [47]; itraconazole vs. fluconazole for 180 days; Overall incidence of proven IFI: itraconazole, 9% vs. fluconazole, 25% (p 0.01); proven/probable IA: itraconazole, 4% vs. fluconazole, 12% (ns); number of deaths related to fungal infection: itraconazole, 9% vs. fluconazole, 18% (ns)	Erratic oral bioavailability and has numerous important drug interactions [48]	IDSA (IC prophylaxis): AI in patients with chemotherapy-induced neutropenia, but less well tolerated than fluconazole/posaconazole
	All yeasts: 1.0	195 patients with acute leukaemia and HCT recipients [41]; itraconazole vs. fluconazole from beginning of chemotherapy until resolution of neutropenia or start of AmB treatment; overall IFI incidence: itraconazole, 11% vs. fluconazole, 12% (ns); proven/probable IA: itraconazole, 9% vs. fluconazole, 11% (ns); number of deaths in patients with IA: itraconazole, 33% vs. fluconazole, 73% (ns)		ECIL-3: CI in leukaemia induction chemotherapy and BI in allo-HCT during initial neutropenic phase and GvHD phase
Fluconazole	All fungi: 128	300 auto/allo-HCT patients [44]; fluconazole vs. placebo for 75 days; *Candida albicans* infection: fluconazole, *n* = 0 vs. placebo, *n* = 18 (p 0.004); fluconazole reduced incidence of superficial fungal infection, fungal colonization and empiric AmB use; OS: fluconazole, 31 deaths vs. placebo, 52 deaths (p 0.004)	Low-cost choice for the prophylaxis of candidiasis and cryptococcosis, relatively few drug interactions [48]	IDSA (IC prophylaxis): AI in patients with chemotherapy-induced neutropenia and stem cell transplant recipients with neutropenia
	All moulds: 256		Lacks activity against filamentous fungi [48]	ECIL-3: CI in leukaemia induction chemotherapy; AI for neutropenic phase and CI for GvHD phase of allo-HCT
	All yeasts: 16			

TABLE 1. continued

Antifungal agent	*In vitro* activity, MIC_{90} (mg/L) [43]	Clinical prophylaxis trials	Advantages and disadvantages	Recommendation from international guidelines[a]
AmB, including liposomal formulations	All fungi: 1.0 All moulds: 2.0 All yeasts: 1.0	271 patients with prolonged neutropenia [42] aerosolized liposomal AmB vs. placebo; Incidence of IA: AmB, 4.3% vs. placebo, 13.6% (p 0.005)	Extended antifungal spectrum, including significant activity against zygomycetes [43,45] Prophylactic use is limited by potentially severe adverse effects [42]	IDSA: – ECIL-3: CI (IV formulations) and BI (liposomal aerosol formulations plus oral fluconazole) in leukaemia induction chemotherapy; CI (IV formulations) in allo-HCT during initial neutropenic and GvHD phases; BII (liposomal aerosol formulations plus oral fluconazole) during initial neutropenic phase

[a]See Table 2A,B for further details on evidence grading systems.
Allo-HCT, allogeneic haematopoietic stem cell transplantation; IFI, invasive fungal infection; ns, not significant; FFS, fungal-free survival; OS, overall survival; IDSA, Infectious Diseases Society of America; ECIL-3, 3rd European Conference on Infection in Leukaemia; IV, intravenous; GvHD, graft-versus-host disease; IA, invasive aspergillosis; AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome; IC, invasive candidiasis; Auto-HCT, autologous haematopoietic stem cell transplantation; AmB, amphotericin B.

of resistant strains in patients who fail prophylaxis. Few alternative options with similar efficacy and tolerability to voriconazole exist for the treatment of potential breakthrough IA; generally, in case of breakthrough IA under azole prophylaxis it is recommended to switch to another class of mould-active antifungals, preferably liposomal amphotericin B [59]. The availability of both oral and intravenous formulations for voriconazole is also a possible advantage in IFI treatment and prophylaxis: whereas oral agents have the potential to be more convenient and cost-effective, the concurrent availability of an intravenous formulation allows for continued uninterrupted treatment in patients with intestinal GvHD, diarrhoea or mucositis—fairly common conditions in haematology patients—who may be unsuitable for oral administration; only oral posaconazole is currently available, and intravenous itraconazole is only available in some countries. In terms of drug bioavailability, antifungal penetration into relevant target tissues is also important. Following administration of oral voriconazole as antifungal prophylaxis, the agent seems to exhibit good tissue penetration into the lungs, the most common primary infection site in IA [62]. Finally, while voriconazole is associated with some important and well-characterized adverse events, its use is generally well tolerated, even for extended periods of time [32,51,63]. Long-term tolerability of antifungal prophylaxis is vital in haematology patients, to allow for the substantial treatment durations often required in this population.

As mentioned above, voriconazole has several potential benefits as a prophylactic agent; however, its use is also associated with a number of concerns and issues. First and foremost, there is the possibility of serious adverse events, such as prolonged visual disturbances, QT-interval prolongation and hepatic toxicity. These events seem to occur mainly in severely ill patients and in those with relevant underlying conditions, and close monitoring of visual and liver function is therefore strongly recommended [49–51]. In addition, there have been a small number of reports of squamous cell carcinoma as well as of melanoma during long-term voriconazole treatment [64,65], potentially associated with the photosensitivity effect of this agent. However, the contribution of voriconazole to the development of squamous cell carcinoma has not been established. Voriconazole and other members of the azole class, such as posaconazole, also give rise to concerns regarding their considerable potential for drug–drug interactions with commonly administered concomitant medications [49–51]. For example, interactions between hepatically metabolized chemotherapy agents (e.g. vinca alkaloids and anthracyclines) and mould-active azoles may result in unacceptable toxicity, unless appropriate dose adjustments can be established [26,66]. Studies have also shown that in combina-

tion with the chemotherapeutic drug/conditioning agent cyclophosphamide, itraconazole may cause clinically significant interactions, including hypertension, neurotoxicity and gastrointestinal toxicity [40]; however, similar interactions have so far not been reported for other mould-active azoles.

Voriconazole prophylaxis may also be complicated by the potential need for voriconazole therapeutic drug monitoring, given the considerable intra-subject variability in the drug's pharmacokinetics. Regular monitoring of voriconazole plasma levels and subsequent dose adjustments have been proposed to improve the efficacy and safety of voriconazole prophylaxis [67–69]. However, so far a plasma concentration range correlating with clinical efficacy could not be formally established in any of the large prospective randomized studies with voriconazole [51]; the non-linear pharmacokinetics of voriconazole probably contribute to the difficulties in determining such a relationship. Voriconazole drug monitoring may have a benefit in terms of safety and compliance issues, because higher plasma levels have been shown to correlate with neurological toxicity [70] and lower levels—which have been shown to correlate with poor efficacy [70]—may be associated with poor compliance or poor intestinal absorption. Another report, however, suggested that voriconazole therapeutic drug monitoring was unlikely to be more useful than routine monitoring of liver function tests in reducing drug-related hepatotoxicity [71]. Other currently available extended-spectrum azoles (i.e. itraconazole and posaconazole) also have issues regarding therapeutic drug monitoring and pharmacokinetic variability, which is particularly problematic in allogeneic HCT recipients with intestinal GvHD who are receiving an oral azole formulation [8,72,73]. In this regard, the clinical judgment of the physician is important. Finally, it has been suggested that the rise in zygomycosis observed at some transplant centres could be associated with the local use of voriconazole prophylaxis. However, this potential correlation remains disputed: such epidemiological shifts may actually be the result of evolving transplant practices (including more diagnostic investigations, more effective anti-*Aspergillus* prophylaxis and changes in immunosuppression) that result in improved patient survival, rather than being the result of selective pressure [51,74].

Evidence from clinical trials

Primary antifungal prophylaxis

Fluconazole has been evaluated in well-designed randomized controlled antifungal prophylaxis studies. In two placebo-controlled, double-blind trials mainly conducted in allogeneic HCT recipients, 400 mg/day fluconazole was significantly more effective than placebo in reducing IFIs and attributable mortality [44,51,75]. Other agents successfully evaluated against placebo for primary antifungal prophylaxis in haematology patients include intravenous [76] and inhaled liposomal amphotericin B, although the latter was only effective for the prevention of pulmonary IA and all patients in the respective study received concomitant fluconazole [42]. Comparative trials of fluconazole against itraconazole for primary antifungal prophylaxis in allogeneic HCT recipients failed to show a survival advantage for itraconazole, despite the latter agent's broader spectrum [47,77,78]. However, some of these studies showed a significant reduction in breakthrough IFIs [47,78] with itraconazole compared with fluconazole. The echinocandin micafungin was found to be superior to fluconazole in reducing suspected, probable, or proven IFIs with equivalent mortality in a combined population of autologous and allogeneic HCT recipients [33]. However, this superiority was achieved mainly through the higher incidence of suspected infections in the fluconazole arm; the incidence of proven and probable IFIs was extremely low in this study (i.e. about 2% in each treatment arm) and did not differ significantly between micafungin and fluconazole [33]. Finally, in allogeneic HCT recipients with GvHD, who constitute a particularly high-risk population, posaconazole was found to be superior to fluconazole in reducing IA incidence and IFI-related mortality. However, this benefit was significant only in patients with acute GvHD, and not in those with chronic GvHD. It should also be noted that in this study 18 patients (6.0%) treated with posaconazole reported serious treatment-related adverse events associated with abnormal liver function (i.e. bilirubinemia, increased hepatic enzymes, increased γ-glutamyltransferase, hepatocellular damage and abnormal hepatic function), compared with ten patients (3.3%) in the fluconazole arm [46]. Another study showed posaconazole to be superior to fluconazole or itraconazole in reducing IFI incidence as well as improving survival when used as primary prophylaxis in acute myeloid leukaemia and myelodysplastic syndrome patients with chemotherapy-induced neutropenia [31].

Recently, two large clinical studies have also evaluated voriconazole as primary antifungal prophylaxis following allogeneic HCT. The first was a randomized, double-blind trial comparing voriconazole (200 mg twice daily) with fluconazole (400 mg daily) in allograft recipients ≥2 years of age who were receiving full-intensity conditioning regimens and were considered to be at standard risk of IFI [34]; patients at the highest risk of IFI were intentionally excluded to minimize the effect of competing non-fungal-related causes of death, a major potential confounder in any study of antifungal prophylaxis [79]. Study prophylaxis was administered for a minimum

duration of 100 days, which could be extended to 180 days for those patients who at day 100 were receiving prednisone (≥1 mg/kg daily) and/or had CD4 T-lymphocyte counts of <200/μL (in case they were recipients of T-cell-depleted grafts). Serum galactomannan levels were evaluated twice weekly for 60 days in all patients and then once or twice weekly until day 100, depending on the presence and severity of GvHD. An intensive diagnostic process was conducted for all patients who exhibited a positive galactomannan assay result, suspicious radiology or signs or symptoms indicative of an IFI. If a patient presented with a possible IFI, empiric antifungal therapy (with liposomal amphotericin B or caspofungin) was permitted for a maximum of 14 days until the outcome of detailed diagnostics became available. The primary endpoint of the study was fungal-free survival at 6 months post-transplant in the intent-to-treat population [34].

After randomization, 295 patients were assigned to fluconazole and 305 to voriconazole. Among the total of 600 patients, most had leukaemia as their underlying condition, in the form of acute myeloid leukaemia (34–44%), acute lymphoid leukaemia (19–22%), or chronic myeloid leukaemia (14–20%); myelodysplastic syndrome (16–17%) and non-Hodgkin's lymphoma (7%) were less common. The median age of the study participants was 43 years (range: 2–65); 92% of patients were older than 18 years, 55% were male, 96% had a matched donor, and 55–57% had received their transplant from a matched related donor. Overall, there were no significant differences between the two arms in terms of baseline demographics, including disease type, IFI risk, or transplant characteristics. Rates of engraftment, acute or chronic GvHD, and of non-fungal infections were also not significantly different between the two treatment groups. All randomized patients were to be followed up for a total of 12 months [34].

Fungal-free survival at 6 months was 78% with voriconazole and 75% with fluconazole, and at 12 months was 64% with voriconazole and 65% with fluconazole. The differences between treatment groups were not significant. There were also no differences in overall survival between the two agents at 6 and 12 months (Fig. 1) [34]. Furthermore, rates of severe AEs and early withdrawal from the study were similar for the two treatment groups. During the course of the trial a total of 28 proven, 33 probable, 18 presumptive (defined as presence of at least one clinical criterion for lower respiratory tract infection, with results from bronchoscopic examination excluding other potential causes), and 75 possible IFIs were recorded. The cumulative incidence rates of proven, probable and presumptive IFI were similar between the two arms: 7.3% for voriconazole and 11.2% for

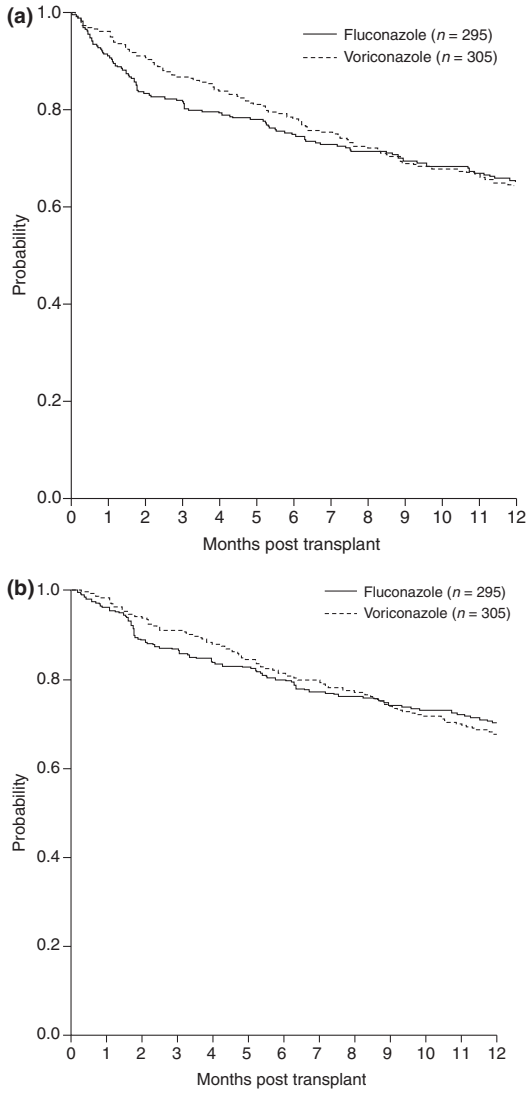

FIG. 1. Kaplan–Meier estimates of fungal-free (proven/probable/presumptive) survival (a) and overall survival (b) up to 12 months in a large, randomized, controlled trial comparing voriconazole and fluconazole for primary prophylaxis of invasive fungal infections in allogeneic haematopoietic stem cell transplant recipients [34]. Reproduced with permission of the American Society of Hematology, from Wingard *et al.* [34]; permission conveyed through Copyright Clearance Center, Inc.

fluconazole at 6 months (p 0.12) and 12.7% and 13.7% at 12 months (p 0.59), respectively. At the 6-month time point, the most common causative pathogens for proven/probable IFIs were *Aspergillus* spp., i.e. in 17 fluconazole and nine voriconazole patients (p 0.09); *Candida* spp. were causative in five patients treated with fluconazole and in three patients treated with voriconazole, zygomycetes in three fluconazole patients and one voriconazole patient, and other fungi in one

patient in each arm [34]. Based on the results of this study, voriconazole and fluconazole seem to have similar efficacy for reducing mortality in standard-risk allograft recipients when used in the context of intensive IFI monitoring and structured empiric antifungal therapy. Interestingly, there was a relatively high rate of such empiric therapy for possible IFI in both arms (voriconazole 24%, fluconazole 30%, p 0.11), which may partially account for the lack of differences between both agents and the low overall incidence of IFI.

These results—i.e. no differences in survival rates but a trend towards reduced frequency of IA—mirror the findings from a clinical trial comparing posaconazole and fluconazole in the same setting. That latter trial exclusively enrolled high-risk allogeneic HCT patients with GvHD, and although crude mortality and total IFI rates were similar for both agents, posaconazole was superior in reducing IA, breakthrough IFIs and attributable mortality [46]. Girmenia *et al.* [80] recently questioned whether the patient population of the voriconazole trial was at sufficiently high risk of IFI when contrasted with the posaconazole study. Of note, exploratory analyses showed that in the higher-risk subpopulation of patients with acute myeloid leukaemia, voriconazole may have significantly improved 6-month fungal-free survival (78% versus 61%, p 0.04) and reduced incidence of IFI (9% versus 21%, p 0.04) compared with fluconazole [34,80].

Based on the outcomes from the large randomized trials discussed so far, it seems that treatment differences between antifungals used for prophylaxis of IFIs in allogeneic HCT recipients are relatively difficult to detect when using crude survival or overall IFI incidence alone as the primary endpoints. This may particularly be the case when the study design permits the use of empirical/pre-emptive therapy for suspected IFIs, a useful approach that mimics clinical reality and has been allowed in all major antifungal prophylaxis trials published to date.

Composite endpoints combining outcomes—such as IFI incidence, survival, other licensed antifungal therapy use, and treatment tolerability—may therefore be a valuable alternative measure for detecting treatment differences in the setting of antifungal prophylaxis in haematology patients. The IMPROVIT study, a large clinical trial evaluating voriconazole against itraconazole as primary prophylaxis in allogeneic HCT recipients, took such an approach [32].

This study was a prospective, phase III, randomized, open-label, multi-centre clinical trial. Eligible patients were ≥12 years of age and were to receive full-intensity or reduced-intensity allogeneic HCT for acute leukaemia, transformed chronic myeloid leukaemia, or failure of lymphoma therapy. Patients were randomly assigned to either voriconazole or itraconazole in a 1:1 ratio and were stratified by donor source (i.e. sibling or unrelated donor) and conditioning regimen (i.e. full or reduced intensity).

Following intravenous loading, both voriconazole and itraconazole were administered orally at 200 mg twice daily. Prophylaxis was to be initiated on the day of stem cell infusion (day 1) until day 100; antifungal prophylaxis could be continued for a further 80 days if predefined IFI risk factors persisted. All patients were followed for ≤180 days. Empirical antifungal therapy could be employed for ≤14 days in case of possible IFI. The primary endpoint of the trial was success of antifungal prophylaxis at day 180, which was defined as fungal-free survival to day 180 without having discontinued study treatment for >14 days in total before day 100 [32].

The modified intent-to-treat population included a total of 224 patients in the voriconazole and 241 in the itraconazole arm. Both treatment groups were similar in terms of baseline characteristics (including underlying disease, conditioning regimen and T-cell depletion) and specific IFI risk factors (i.e. the incidence of overall GvHD as well as liver-specific GvHD). Superiority of voriconazole was concluded for the primary endpoint: success of antifungal prophylaxis at day 180 was attained by 49% of voriconazole and 33% of itraconazole patients (p <0.01) and did not vary across randomization strata. Voriconazole was also superior to itraconazole at day 100 (Fig. 2) [32]. The superiority of voriconazole was mostly the result of differences in the numbers of patients who received the per-protocol duration of prophylaxis (voriconazole: 54%; itraconazole: 39%; p <0.01).

The most common reasons for early treatment discontinuation were adverse events (23.2%) and study drug intoler-

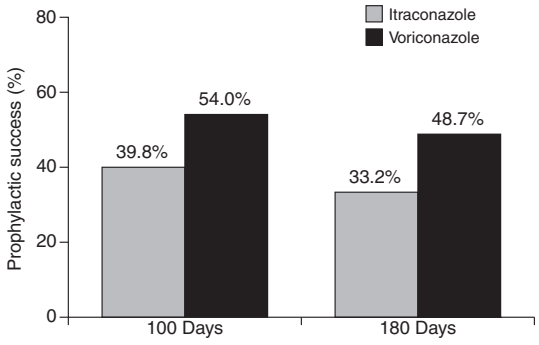

FIG. 2. Prophylactic success (composite endpoint combining fungal-free survival and sufficient duration of prophylaxis; adjusted for conditioning regimen and donor relatedness) at day 100 and day 180 in a large, randomized, controlled trial comparing voriconazole and itraconazole for primary prophylaxis of invasive fungal infections in allogeneic haematopoietic stem cell transplant recipients [32]. Voriconazole was superior (p <0.01) to itraconazole at both time points.

ance (21.6%) in the case of itraconazole and the occurrence of adverse events (29.9%) with voriconazole; side effects that limited itraconazole therapy were mostly related to gastrointestinal intolerance. Itraconazole-treated patients had almost 30 days less of prophylaxis, with a median treatment duration of 68 days compared with 96 days with voriconazole ($p < 0.01$) [32]. These results suggest that voriconazole has better long-term treatment tolerance than itraconazole. As allogeneic HCT recipients probably require sustained durations of antifungal prophylaxis [15,32], this difference may represent an important advantage of voriconazole over itraconazole.

Both treatment groups had almost identical crude survival rates at day 100 (92% in each group) and day 180 (82% for voriconazole and 81% for itraconazole), with the 1-year survival rates being similar (voriconazole: 74%; itraconazole: 67%; p 0.17). There were also no statistically significant differences in terms of proven/probable IFIs overall, documented IA in particular, breakthrough IFIs, and treatment-emergent IFIs, even though there was a trend in all of these secondary endpoints that appeared to favour voriconazole. A total of eight IFIs were recorded during the trial: one probable and two proven IFI in the voriconazole and four probable and one proven IFI in the itraconazole arm. There were no instances of invasive zygomycosis in either treatment group. Of note, the use of other licensed antifungal therapies, in particular caspofungin and liposomal amphotericin B, was significantly higher in the itraconazole arm (42% versus 30%; $p < 0.01$); furthermore, about 14% of patients initially randomized to itraconazole were switched to voriconazole as an 'other licensed antifungal therapy' at some point during the study period [32]. This more frequent use of non-study, mould-active systemic antifungals in itraconazole patients may partially explain the lack of significant differences in IFI and survival rates between the two treatments, and further underscores the advantage of voriconazole over itraconazole reported in this study.

Similar outcomes were observed in patients who developed grade II to IV and/or extensive chronic GvHD during the study (voriconazole, $n = 62$; itraconazole, $n = 64$) [81]. Baseline characteristics of patients who went on to develop GvHD were generally similar to those of patients who did not. Success of prophylaxis at day 180 in the subpopulation with GvHD was also significantly higher with voriconazole (50% versus 30%; p 0.03). The average duration of study prophylaxis was 107 versus 84 days ($p < 0.01$) and the proportions of patients with sufficient duration of prophylaxis were 60% versus 42% (p 0.05) for voriconazole and itraconazole, respectively. Similar to the overall study population, there were no significant treatment differences in mortality and IFI incidence. In the subpopulation with GvHD, adverse events leading to discontinuation of study treatment were significantly more frequent with itraconazole (53% versus 34%; $p < 0.05$), especially those of a gastrointestinal nature (16% versus 0%; $p < 0.01$) [81].

For the overall study population, pharmacokinetic data were available from 52% of voriconazole and 54% of itraconazole patients. Among the former, 15% had trough levels, with a median concentration of 0.85 mg/L; trough levels were >0.5 mg/L in 65% of these patients and >1.0 mg/L in 38%. In itraconazole patients, 10% had trough levels with a median concentration of 0.89 mg/L; 83% and 46% of these patients, respectively, had trough levels >0.5 and >1.0 mg/L [32].

With regard to overall patient safety, treatment-related gastrointestinal adverse events (nausea, vomiting and diarrhoea) occurred more frequently with itraconazole ($p \leq 0.01$ in all cases), whereas visual side effects were only reported in voriconazole patients (5%; $p < 0.01$). Hepatotoxicity, including liver function test abnormalities, was also more common with voriconazole (13% versus 5%; $p < 0.01$). The average number of treatment-related adverse events per 30 days of treatment was comparable (p 0.53) between voriconazole (1.7; 95% CI, 1.1–2.2) and itraconazole (2.0; 95% CI, 1.3–2.6) [32]. Both agents therefore appear to have had a similar frequency of adverse events overall. This assumption is further supported by the results of a validated patient satisfaction questionnaire showing that treatment side effect scores at day 14 were similar for both agents, although the convenience and global satisfaction scores favoured voriconazole.

The authors concluded that primary prophylaxis with voriconazole effectively prevents IFI following allogeneic HCT, with acceptable safety. The superiority of voriconazole in the primary endpoint appeared to be driven mainly by its better long-term tolerability, which was also reflected in higher patient-reported treatment satisfaction scores [32]. The ability to tolerate the chosen prophylactic agent for extended treatment durations is an important consideration, given the fact that IFIs (especially IA) can occur up to 6 months after transplant [82].

A number of other recent studies further support the efficacy of voriconazole for the primary prevention of IFIs (especially IA) in HCT recipients at various risks of systemic fungal disease, as well as in patients with acute myeloid leukaemia. These studies were mostly retrospective/observational [68,83–87]; a randomized, placebo-controlled trial was stopped prematurely (as the result of availability of new data that made further comparison with placebo unethical) [88]. Preliminary favourable outcomes observed among leukaemia patients merit further prospective evaluation of voriconazole

as primary antifungal prophylaxis in this setting, in particular because voriconazole may result in less toxicity than other broad-spectrum azoles when administered concomitantly with chemotherapy drugs that are substrates for cytochrome P450 isozymes [66].

Given the potential cost implications of long-term antifungal prophylaxis, pharmacoeconomic data on the use of voriconazole in this setting would be of interest. Unfortunately, no such data are currently available. Other extended-spectrum azoles were demonstrated to be cost-effective compared with fluconazole for primary IFI prophylaxis in HCT recipients with GvHD and in other specific groups of neutropenic haematology patients [89–92]. However, some of these analyses have potential limitations [35], and the cost-effectiveness of voriconazole prophylaxis remains to be elucidated by relevant studies.

Secondary antifungal prophylaxis

In HCT recipients and haematological malignancy patients who survived a previous IFI, its recurrence or the development of a new IFI are major causes of morbidity and mortality [1,93]. The rate of IFI relapse following allogeneic HCT is between 19 and 33% [94–96] and about 16% in patients with acute myeloid leukaemia who undergo further myelosuppressive chemotherapy [1]; reactivation rates as high as 52% have been reported during subsequent periods of neutropenia in adults with acute non-lymphocytic leukaemia [97]. In acute myeloid leukaemia patients with previous pulmonary IFI who receive additional antineoplastic chemotherapy, the relapse risk is increased in the presence of only partial resolution of the previous IFI, prolonged neutropenia, earlier antibiotic therapy and high-dose cytarabine [1,98]. Fortunately, in these patients administration of broad-spectrum antifungal agents has shown some potential in the prevention of IFI relapse or progression, so permitting the vital continuation of treatment even in the presence of residual IFI [99,100]. The term 'secondary prophylaxis' should only be applied to trials in which all patients have no evidence of active IFI at the time of enrolment; in cases where patients have continued signs and symptoms of invasive fungal disease, this is more accurately described as treatment of IFI in partial remission.

Until recently, only limited clinical data were available in this setting, both for voriconazole [98,101] and for other potential prophylactic agents [102,103]. The use of voriconazole as secondary antifungal prophylaxis was originally evaluated in a retrospective analysis of leukaemia patients with previous IA (n = 10) or invasive candidiasis (n = 1) [98]. Nine of these 11 patients underwent allogeneic HCT, whereas the rest received consolidation therapy for acute leukaemia. All were given voriconazole (400 mg daily) intravenously or orally for a duration of 44–245 days. Encouragingly, no relapse of IFI was reported and the scheduled treatment was delayed in only a single case. Furthermore, with the exception of one patient who experienced visual disturbances and another with abnormal liver function tests secondary to hepatic GvHD, voriconazole appeared to be well tolerated. The authors concluded that voriconazole may be of value as secondary prophylaxis in leukaemia patients during at-risk periods and recommended prospective trials [98]. A comparable retrospective study of oral voriconazole (200 mg twice daily) was later conducted in patients with a previous diagnosis of possible (n = 20) or proven (n = 2) IFI, who subsequently received further treatment for haematological malignancy [101]; however, it should be noted that most patients only had partial remission of their IFI at enrolment. Similarly, a small, prospective, open-label trial evaluating liposomal amphotericin B followed by oral voriconazole for secondary prophylaxis of IA after allogeneic HCT in paediatric patients also enrolled mostly patients (nine of 11) with merely partial remission of their IFI at the time of transplantation [104]. Of the eight patients who survived to day 180 after transplant, six showed complete resolution of pulmonary infiltrates, one partial resolution, and one ongoing resolution. However, because of the nature of the study population, this trial cannot be considered a true secondary prophylaxis study.

A much larger prospective, open-label, multicentre study of secondary prophylaxis with voriconazole was recently published, focusing on the prevention of recurrent IFI in adult allogeneic HCT recipients [93]. Study participants were required to have had a proven/probable IFI ≤12 months before transplant, according to modified consensus criteria, and could receive allogeneic HCT for any disease and with any conditioning regimen. Patients with evidence of active IFI, a history of zygomycosis, previous failure of voriconazole in antifungal therapy, or significant hepatic or renal impairment were excluded. Voriconazole was initiated ≥48 h after completion of conditioning chemotherapy and ≤3 days before stem cell infusion. Antifungal prophylaxis was planned for a minimum duration of 100 days and could be extended by ≤50 days in case of neutropenia, recent administration of immunosuppressants, or of anti-thymocyte globulin at day 100; patients could switch freely between the intravenous and oral formulations, and were followed for at least 12 months. The primary efficacy endpoint of the study was the incidence of proven/probable IFI at 12 months [93].

Of the 45 patients enrolled, 91% had acute leukaemia as their underlying condition. Haematological disease was in first complete remission in 53%. Previous IFIs were proven IA (n = 6), probable IA (n = 25), proven invasive candidiasis

(*n* = 5), other proven IFI (*n* = 3), or other probable IFI (*n* = 3). In the remaining three patients, a previous systemic fungal infection could not be confirmed. It should be noted that 78% of all patients had received voriconazole as treatment for their previous IFI; the median time between resolution of previous IFI and the date of HCT was 59 days (range: 3–311 days). The median duration of subsequent voriconazole prophylaxis was 94 days (range: 5–180 days). Eleven patients (24%) had died at 12 months' follow-up, only one as the result of an IFI. A total of three IFIs occurred after transplant: two relapses (one candidaemia and one fatal scedosporiosis) and one new zygomycosis in a patient with previous IA. Although 31/42 (74%) of the enrolled patients had previous proven or probable IA, no case of IA was observed after transplant in the entire cohort. Overall, the 1-year cumulative IFI incidence was about 7%, considerably lower than the relapse rate reported in previous series. Treatment-related adverse events (liver toxicity) led to the withdrawal of two patients from the study [93].

Finally, a recent, small case series from Japan assessed voriconazole as secondary prophylaxis in 15 patients with acute leukaemia. All patients had previously been successfully treated with oral voriconazole for a primary pulmonary IFI, and subsequently received voriconazole as secondary prophylaxis during additional rounds of chemotherapy (35 courses in total). In this study, 93% of patients successfully completed their planned leukaemia therapy without significant toxicity or suspected IFI. The authors suggested that, based on their results and a review of the literature, voriconazole may be a useful option for secondary antifungal prophylaxis during myelosuppressive therapy [99]. Based on the body of available data, secondary prophylaxis with voriconazole therefore appears to be safe and effective in preventing the recurrence of IFI following allogeneic HSCT, and possibly also in patients with haematological malignancy undergoing cancer chemotherapy [93,98,99,101,104].

Guidelines on antifungal prophylaxis

Important European guidelines on antifungal prophylaxis include those recently released by the 3rd European Conference on Infections in Leukaemia (ECIL-3) [56]. ECIL-3 uses the original Infectious Diseases Society of America (IDSA) grading system for quality of evidence and strength of recommendations (see Table 2A for details). These consensus recommendations divide high-risk haematology patients into three groups for the purpose of assigning the most appropriate agent for primary antifungal prophylaxis (Fig. 3) [56]. During induction chemotherapy for acute leukaemia, for example, the most strongly recommended agent is posaconazole (AI grading of evidence), followed by aerosolized liposomal amphotericin B in combination with fluconazole (BI), fluconazole (CI), itraconazole (CI) and polyenes (CI). The second patient group consists of allogeneic HCT recipients during the neutropenic phase, for whom voriconazole (provisional AI, pending the final publication of the randomized studies comparing voriconazole with fluconazole and itraconazole [32,34]) and fluconazole (AI) are most strongly recommended; alternatives include itraconazole (BI), aerosolized

TABLE 2. Quality of evidence and strength of recommendations used in (A) the Infectious Diseases Society of America (IDSA) guidelines [59,105] and in (B) the updated European Conference on Infections in Leukaemia (ECIL)-3 guidelines [56]

Quality of evidence	Strength of recommendations
(A) IDSA guidelines	
I: Evidence from at least one properly randomized, controlled trial	A: Good evidence to support recommendation
II: Evidence from at least one well-designed clinical trial without randomization; cohort or case–controlled analytic studies (preferably from more than one centre); multiple time-series studies; or dramatic results from uncontrolled experiments	B: Moderate evidence to support recommendation
III: Evidence from opinions of respected authorities based on clinical experience, descriptive studies or expert committees reports	C: Poor evidence to support recommendation
(B) ECIL-3 guidelines	
I: Evidence from at least one well-executed randomized trial	A: Strongly recommended—strong evidence for efficacy and substantial clinical benefit
II: Evidence from at least one well-designed clinical trial without randomization; cohort or case–controlled analytic studies (preferably from more than one centre); multiple time-series studies; or dramatic results from uncontrolled experiments	B: Generally recommended—strong/moderate evidence for efficacy, but only limited clinical benefit
III: Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or expert committees reports	C: Optional—insufficient evidence for efficacy; or efficacy does not outweigh possible adverse consequences (for example, drug toxicity or interactions) or cost of chemoprophylaxis or alternative approaches
	D: Generally not recommended—moderate evidence against efficacy or for adverse outcome
	E: Never recommended—strong evidence against efficacy or for adverse outcome

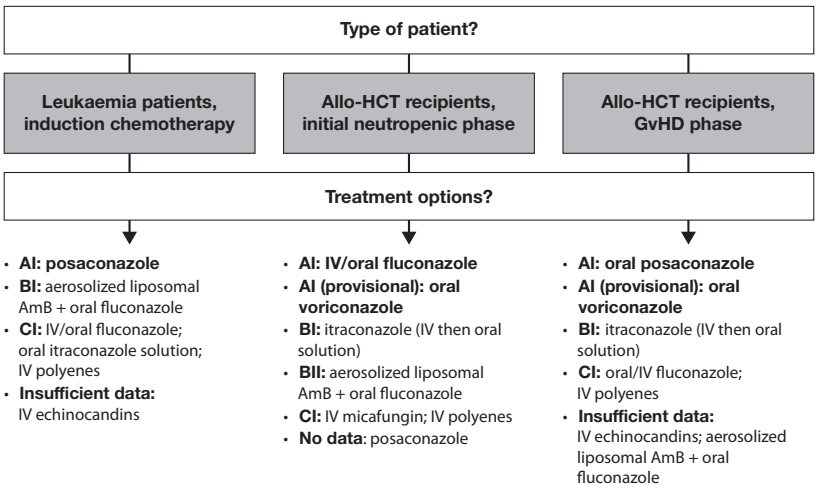

FIG. 3. Patient risk stratification and treatment recommendations for primary antifungal prophylaxis in haematology patients as per the ECIL-3 guidelines [56]. AmB, amphotericin B; GvHD, graft-versus-host disease; HCT, haematopoietic stem cell transplant; IV, intravenous.

liposomal amphotericin B in combination with fluconazole (BII), polyenes (CI) and micafungin (CI). Finally, for allogeneic HCT patients with GvHD, posaconazole (AI) and voriconazole (provisional AI, pending the final publication of the randomized studies comparing voriconazole with fluconazole and itraconazole [32,34]) are suggested as the first-line choices for primary prophylaxis, followed by itraconazole (BI), fluconazole (CI) and polyenes (CI). The guidelines suggest that serum drug concentrations of posaconazole and itraconazole be monitored irrespective of group, to ensure therapeutic levels of these agents. The ECIL-3 recommendations suggest the use of secondary antifungal prophylaxis during an episode of prolonged neutropenia or severe immunosuppression following a previous documented IFI (AII grading). No particular antifungal is suggested as first choice in this setting; rather, selection of an appropriate prophylactic drug should be based on the specific pathogen causative of the previous IFI and the response to antifungal therapy during that episode [56].

Guidelines on antifungal prophylaxis in haematology patients have also been jointly released by the Center for International Blood and Marrow Transplant Research, the European Blood and Marrow Transplant Group, the American Society of Blood and Marrow Transplantation, the Canadian Blood and Marrow Transplant Group, the IDSA, the Centers for Disease Control and Prevention, and a number of other societies [106,107]; these guidelines also use the original IDSA evidence grading system (Table 2A). These guidelines recommend fluconazole (at doses ≥200 mg/day) as the drug of choice for preventing invasive candidiasis, other than that caused by *Candida krusei* or *Candida glabrata*, in allogeneic HCT recipients in the period before engraftment (AI grading); micafungin can be used as an alternative in this setting (BI). For the prevention of invasive candidiasis during the post-engraftment period, both voriconazole (BI) and posaconazole (BI) are recommended as suitable options. The guidelines also recommend the chemoprophylaxis of mould infections in patients at higher risk of such IFIs (BI), either with itraconazole (BI), posaconazole (in patients with GvHD; BI), or aerosolized liposomal amphotericin B (BII). The group did not comment on voriconazole as primary antifungal prophylaxis in HCT patients, because the results of the clinical trials comparing voriconazole with fluconazole [34] and itraconazole [32] were not available at the time. Finally, secondary prophylaxis with a mould-active agent is recommended in HCT recipients with previous IA (AII), and voriconazole is listed as a specific option in this setting (AII) [106,107]. Other key international guidelines include those developed by the IDSA on the management of IA, which are based on the revised IDSA evidence grading system (see Table 2B for details); these guidelines give an AI grading to posaconazole for primary prophylaxis in HCT recipients with GvHD and neutropenic patients with acute myeloid leukaemia or myelodysplastic syndrome, who are at high risk for IA [59].

Most current clinical guidelines recommend posaconazole as the main choice for primary antifungal prophylaxis in key high-risk populations, i.e. during induction chemotherapy for leukaemia and in allogeneic HCT recipients during the GvHD phase [56,107,108]. However, although posaconazole prophylaxis yielded clear benefits over fluconazole in some populations, it is not apparent whether any single mould-active agent is superior for the prevention of IFIs [35]. Other mould-active antifungals, such as voriconazole, may therefore also be valuable options in these settings.

Used as primary antifungal prophylaxis in allogeneic HCT recipients, voriconazole and posaconazole share a number of similarities: both are effective in patients with post-transplant GvHD, may require therapeutic drug monitoring to ensure efficacy of antifungal prophylaxis, are available as oral formulations, and are clinically active against moulds as well as yeasts. Furthermore, both voriconazole and posaconazole share gastrointestinal and hepatic side effects as some of their key treatment-related adverse events [49,50]. Similar to the known safety profile of voriconazole [32], posaconazole has been associated with prophylaxis-related hepatotoxicity [46]. However, there are also a number of differences between the two agents. Unlike voriconazole, posaconazole could prevent invasive zygomycosis, even though this protection is not absolute [109]. On the other hand, voriconazole is available as an intravenous formulation to allow continued treatment in case of issues with oral absorption (an intravenous formulation of posaconazole is currently in development), has been successfully evaluated against another mould-active agent in allogeneic HCT recipients, is widely regarded as the reference standard for treating IA (the most prevalent IFI in this setting), and has also been shown to be effective in HCT patients without GvHD. Furthermore, although data exist on the efficacy and safety of prophylactic voriconazole in young children [34], there are currently no prospective trial data for posaconazole in patients younger than 13 years old. Future recommendations on antifungal prophylaxis in haematology patients can therefore be expected to take into account the results of recent studies with voriconazole.

Conclusion

Based on a growing body of data, voriconazole appears to be effective for the primary and secondary prevention of IFIs in haematology patients, in particular HCT recipients. Voriconazole is generally safe and well tolerated in these populations, in accordance with its known overall safety profile. Randomized controlled trials evaluating voriconazole as primary antifungal prophylaxis in neutropenic patients treated for haematological malignancies merit implementation. Furthermore, prospective epidemiological studies assessing the possible impact of voriconazole prophylaxis on the incidence of zygomycosis may also be of value, as would be investigations to establish a potential therapeutic range of voriconazole plasma concentrations and possible dose adjustments during concomitant treatment with hepatically metabolized chemotherapy.

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Transparency Declaration

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References

1. Cornely OA, Bohme A, Reichert D *et al.* Risk factors for breakthrough invasive fungal infection during secondary prophylaxis. *J Antimicrob Chemother* 2008; 61: 939–946.
2. Fukuda T, Boeckh M, Carter RA *et al.* Risks and outcomes of invasive fungal infections in recipients of allogeneic hematopoietic stem cell transplants after nonmyeloablative conditioning. *Blood* 2003; 102: 827–833.
3. Lass-Florl C. The changing face of epidemiology of invasive fungal disease in Europe. *Mycoses* 2009; 52: 197–205.
4. Marr KA, Carter RA, Crippa F, Wald A, Corey L. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. *Clin Infect Dis* 2002; 34: 909–917.
5. Ninin E, Milpied N, Moreau P *et al.* Longitudinal study of bacterial, viral, and fungal infections in adult recipients of bone marrow transplants. *Clin Infect Dis* 2001; 33: 41–47.
6. Upton A, Kirby KA, Carpenter P, Boeckh M, Marr KA. Invasive aspergillosis following hematopoietic cell transplantation: outcomes and prognostic factors associated with mortality. *Clin Infect Dis* 2007; 44: 531–540.
7. Bhatti Z, Shaukat A, Almyroudis NG, Segal BH. Review of epidemiology, diagnosis, and treatment of invasive mould infections in allogeneic hematopoietic stem cell transplant recipients. *Mycopathologia* 2006; 162: 1–15.
8. Ben-Ami R, Lewis RE, Kontoyiannis DP. Invasive mould infections in the setting of hematopoietic cell transplantation: current trends and new challenges. *Curr Opin Infect Dis* 2009; 22: 376–384.
9. Wald A, Leisenring W, van Burik JA, Bowden RA. Epidemiology of *Aspergillus* infections in a large cohort of patients undergoing bone marrow transplantation. *J Infect Dis* 1997; 175: 1459–1466.
10. Pagano L, Caira M, Nosari A *et al.* Fungal infections in recipients of hematopoietic stem cell transplants: results of the SEIFEM B-2004 study – Sorveglianza Epidemiologica Infezioni Fungine Nelle Emopatie Maligne. *Clin Infect Dis* 2007; 45: 1161–1170.

11. Marr KA. Fungal infections in oncology patients: update on epidemiology, prevention, and treatment. *Curr Opin Oncol* 2010; 22: 138–142.
12. Sipsas NV, Lewis RE, Tarrand J *et al.* Candidemia in patients with hematologic malignancies in the era of new antifungal agents (2001–2007): stable incidence but changing epidemiology of a still frequently lethal infection. *Cancer* 2009; 115: 4745–4752.
13. Kontoyiannis DP, Marr KA, Park BJ *et al.* Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. *Clin Infect Dis* 2010; 50: 1091–1100.
14. Neofytos D, Horn D, Anaissie E *et al.* Epidemiology and outcome of invasive fungal infection in adult hematopoietic stem cell transplant recipients: analysis of Multicenter Prospective Antifungal Therapy (PATH) Alliance registry. *Clin Infect Dis* 2009; 48: 265–273.
15. Bow EJ. Long-term antifungal prophylaxis in high-risk hematopoietic stem cell transplant recipients. *Med Mycol* 2005; 43 (suppl 1): S277–S287.
16. Almirante B, Rodriguez D, Park BJ *et al.* Epidemiology and predictors of mortality in cases of *Candida* bloodstream infection: results from population-based surveillance, Barcelona, Spain, from 2002 to 2003. *J Clin Microbiol* 2005; 43: 1829–1835.
17. Cornely OA, Maertens J, Bresnik M *et al.* Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad trial). *Clin Infect Dis* 2007; 44: 1289–1297.
18. Cornillet A, Camus C, Nimubona S *et al.* Comparison of epidemiological, clinical, and biological features of invasive aspergillosis in neutropenic and nonneutropenic patients: a 6-year survey. *Clin Infect Dis* 2006; 43: 577–584.
19. Fourneret-Vivier A, Lebeau B, Mallaret MR *et al.* Hospital-wide prospective mandatory surveillance of invasive aspergillosis in a French teaching hospital (2000–2002). *J Hosp Infect* 2006; 62: 22–28.
20. Herbrecht R, Denning DW, Patterson TF *et al.* Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002; 347: 408–415.
21. Lass-Florl C, Griff K, Mayr A *et al.* Epidemiology and outcome of infections due to *Aspergillus terreus*: 10-year single centre experience. *Br J Haematol* 2005; 131: 201–207.
22. Pagano L, Caira M, Candoni A *et al.* The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. *Haematologica* 2006; 91: 1068–1075.
23. Pagano L, Caira M, Candoni A *et al.* Invasive aspergillosis in patients with acute myeloid leukemia: a SEIFEM-2008 registry study. *Haematologica* 2010; 95: 644–650.
24. Tortorano AM, Kibbler C, Peman J, Bernhardt H, Klingspor L, Grillot R. Candidaemia in Europe: epidemiology and resistance. *Int J Antimicrob Agents* 2006; 27: 359–366.
25. Michallet M, Ito JI. Approaches to the management of invasive fungal infections in hematologic malignancy and hematopoietic cell transplantation. *J Clin Oncol* 2009; 27: 3398–3409.
26. Wirk B, Wingard JR. Current approaches in antifungal prophylaxis in high risk hematologic malignancy and hematopoietic stem cell transplant patients. *Mycopathologia* 2009; 168: 299–311.
27. Chandrasekar P. Prophylaxis against *Aspergillus* is not perfect: problems and perils in stem cell transplantation. *Med Mycol* 2009; 47 (suppl 1): S349–S354.
28. Marr KA. Primary antifungal prophylaxis in hematopoietic stem cell transplant recipients: clinical implications of recent studies. *Curr Opin Infect Dis* 2008; 21: 409–414.
29. Ruping MJ, Vehreschild JJ, Cornely OA. Patients at high risk of invasive fungal infections: when and how to treat. *Drugs* 2008; 68: 1941–1962.
30. Ruping MJ, Vehreschild JJ, Cornely OA. Primary antifungal prophylaxis in acute myeloblastic leukemia and myelodysplastic syndrome – still an open question? *Leuk Lymphoma* 2010; 51: 20–26.
31. Cornely OA, Maertens J, Winston DJ *et al.* Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med* 2007; 356: 348–359.
32. Marks DI, Pagliuca A, Kibbler CC *et al.* Voriconazole versus itraconazole for antifungal prophylaxis following allogeneic stem cell transplanation. *Br J Haematol* 2011; 155: 318–327.
33. van Burik JA, Ratanatharathorn V, Stepan DE *et al.* Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. *Clin Infect Dis* 2004; 39: 1407–1416.
34. Wingard JR, Carter SL, Walsh TJ *et al.* Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. *Blood* 2010; 116: 5111–5118.
35. Wolf J, Slavin MA. Risk-based antifungal prophylaxis in hematologic malignancy and stem cell transplantation. *Curr Infect Dis Rep* 2009; 11: 420–426.
36. Maschmeyer G. The changing face of febrile neutropenia-from monotherapy to moulds to mucositis. Prevention of mould infections. *J Antimicrob Chemother* 2009; 63 (suppl 1): i27–i30.
37. Tamura K, Drew R. Antifungal prophylaxis in adult hematopoietic stem cell transplant recipients. *Drugs Today (Barc)* 2008; 44: 515–530.
38. Bochud PY, Calandra T. A new step toward individualized antifungal prevention in hematopoietic stem cell transplantation. *Clin Infect Dis* 2009; 49: 733–735.
39. De PB, Donnelly JP. Prophylaxis and aspergillosis – has the principle been proven? *N Engl J Med* 2007; 356: 409–411.
40. Marr KA, Leisenring W, Crippa F *et al.* Cyclophosphamide metabolism is affected by azole antifungals. *Blood* 2004; 103: 1557–1559.
41. Oren I, Rowe JM, Sprecher H *et al.* A prospective randomized trial of itraconazole vs fluconazole for the prevention of fungal infections in patients with acute leukemia and hematopoietic stem cell transplant recipients. *Bone Marrow Transplant* 2006; 38: 127–134.
42. Rijnders BJ, Cornelissen JJ, Slobbe L *et al.* Aerosolized liposomal amphotericin B for the prevention of invasive pulmonary aspergillosis during prolonged neutropenia: a randomized, placebo-controlled trial. *Clin Infect Dis* 2008; 46: 1401–1408.
43. Sabatelli F, Patel R, Mann PA *et al. In vitro* activities of posaconazole, fluconazole, itraconazole, voriconazole, and amphotericin B against a large collection of clinically important molds and yeasts. *Antimicrob Agents Chemother* 2006; 50: 2009–2015.
44. Slavin MA, Osborne B, Adams R *et al.* Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation – a prospective, randomized, double-blind study. *J Infect Dis* 1995; 171: 1545–1552.
45. Sun QN, Fothergill AW, McCarthy DI, Rinaldi MG, Graybill JR. *In vitro* activities of posaconazole, itraconazole, voriconazole, amphotericin B, and fluconazole against 37 clinical isolates of zygomycetes. *Antimicrob Agents Chemother* 2002; 46: 1581–1582.
46. Ullmann AJ, Lipton JH, Vesole DH *et al.* Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med* 2007; 356: 335–347.
47. Winston DJ, Maziarz RT, Chandrasekar PH *et al.* Intravenous and oral itraconazole versus intravenous and oral fluconazole for long-term antifungal prophylaxis in allogeneic hematopoietic stem-cell transplant recipients. A multicenter randomized trial. *Ann Intern Med* 2003; 138: 705–713.
48. Zonios DI, Bennett JE. Update on azole antifungals. *Semin Respir Crit Care Med* 2008; 29: 198–210.
49. Pfizer, Inc. *Vfend [US prescribing information]*. New York, NY: Pfizer, Inc., 2011.

50. European Medicines Agency. *Vfend—product information*. European Medicines Agency, Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000387/human_med_001135.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d124 (accessed on 7 September 2011).
51. Cecil JA, Wenzel RP. Voriconazole: a broad-spectrum triazole for the treatment of invasive fungal infections. *Expert Rev Hematol* 2009; 2: 237–254.
52. Kullberg BJ, Sobel JD, Ruhnke M *et al.* Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial. *Lancet* 2005; 366: 1435–1442.
53. Perfect JR, Marr KA, Walsh TJ *et al.* Voriconazole treatment for less-common, emerging, or refractory fungal infections. *Clin Infect Dis* 2003; 36: 1122–1131.
54. Troke P, Aguirrebengoa K, Arteaga C *et al.* Treatment of scedosporiosis with voriconazole: clinical experience with 107 patients. *Antimicrob Agents Chemother* 2008; 52: 1743–1750.
55. Walsh TJ, Lutsar I, Driscoll T *et al.* Voriconazole in the treatment of aspergillosis, scedosporiosis and other invasive fungal infections in children. *Pediatr Infect Dis J* 2002; 21: 240–248.
56. Maertens J, Marchetti O, Herbrecht R *et al.* European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3 – 2009 update. *Bone Marrow Transplant* 2011; 46: 709–718.
57. Guidelines on the management of invasive fungal infection during therapy for haematological malignancy. BCSH Guidelines Home Page. http://www.bcshguidelines.com/documents/fungal_infection_bcsh_2008.pdf (accessed on 7 September 2011).
58. Thursky KA, Playford EG, Seymour JF *et al.* Recommendations for the treatment of established fungal infections. *Intern Med J* 2008; 38: 496–520.
59. Walsh TJ, Anaissie EJ, Denning DW *et al.* Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis* 2008; 46: 327–360.
60. Bohme A, Ruhnke M, Buchheidt D *et al.* Treatment of invasive fungal infections in cancer patients – recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). *Ann Hematol* 2009; 88: 97–110.
61. Freemantle N, Tharmanathan P, Herbrecht R. Systematic review and mixed treatment comparison of randomized evidence for empirical, pre-emptive and directed treatment strategies for invasive mould disease. *J Antimicrob Chemother* 2011; 66 (suppl 1): i25–i35.
62. Capitano B, Potoski BA, Husain S *et al.* Intrapulmonary penetration of voriconazole in patients receiving an oral prophylactic regimen. *Antimicrob Agents Chemother* 2006; 50: 1878–1880.
63. Queiroz-Telles F, Goldani LZ, Schlamm HT, Goodrich JM, Espinel-Ingroff A, Shikanai-Yasuda MA. An open-label comparative pilot study of oral voriconazole and itraconazole for long-term treatment of paracoccidioidomycosis. *Clin Infect Dis* 2007; 45: 1462–1469.
64. Cowen EW, Nguyen JC, Miller DD *et al.* Chronic phototoxicity and aggressive squamous cell carcinoma of the skin in children and adults during treatment with voriconazole. *J Am Acad Dermatol* 2010; 62: 31–37.
65. Miller DD, Cowen EW, Nguyen JC, McCalmont TH, Fox LP. Melanoma associated with long-term voriconazole therapy: a new manifestation of chronic photosensitivity. *Arch Dermatol* 2010; 146: 300–304.
66. Whittle AM, Ali S. Primary prophylaxis with voriconazole in patients receiving induction chemotherapy on the MRC adult acute lymphoblastic leukaemia trial (UK-ALL XII) to avoid itraconazole-enhanced vinca neurotoxicity. *Int J Lab Hematol* 2008; 30: 173–174.
67. Trifilio S, Pennick G, Pi J *et al.* Monitoring plasma voriconazole levels may be necessary to avoid subtherapeutic levels in hematopoietic stem cell transplant recipients. *Cancer* 2007; 109: 1532–1535.
68. Trifilio S, Singhal S, Williams S *et al.* Breakthrough fungal infections after allogeneic hematopoietic stem cell transplantation in patients on prophylactic voriconazole. *Bone Marrow Transplant* 2007; 40: 451–456.
69. Trifilio SM, Yarnold PR, Scheetz MH, Pi J, Pennick G, Mehta J. Serial plasma voriconazole concentrations after allogeneic hematopoietic stem cell transplantation. *Antimicrob Agents Chemother* 2009; 53: 1793–1796.
70. Pascual A, Calandra T, Bolay S, Buclin T, Bille J, Marchetti O. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. *Clin Infect Dis* 2008; 46: 201–211.
71. Tan K, Brayshaw N, Tomaszewski K, Troke P, Wood N. Investigation of the potential relationships between plasma voriconazole concentrations and visual adverse events or liver function test abnormalities. *J Clin Pharmacol* 2006; 46: 235–243.
72. Hope WW, Billaud EM, Lestner J, Denning DW. Therapeutic drug monitoring for triazoles. *Curr Opin Infect Dis* 2008; 21: 580–586.
73. Lebeaux D, Lanternier F, Elie C *et al.* Therapeutic drug monitoring of posaconazole: a monocentric study with 54 adults. *Antimicrob Agents Chemother* 2009; 53: 5224–5229.
74. Pongas GN, Lewis RE, Samonis G, Kontoyiannis DP. Voriconazole-associated zygomycosis: a significant consequence of evolving antifungal prophylaxis and immunosuppression practices? *Clin Microbiol Infect* 2009; 15 (suppl 5): 93–97.
75. Goodman JL, Winston DJ, Greenfield RA *et al.* A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. *N Engl J Med* 1992; 326: 845–851.
76. Penack O, Schwartz S, Martus P *et al.* Low-dose liposomal amphotericin B in the prevention of invasive fungal infections in patients with prolonged neutropenia: results from a randomized, single-center trial. *Ann Oncol* 2006; 17: 1306–1312.
77. Glasmacher A, Cornely O, Ullmann AJ *et al.* An open-label randomized trial comparing itraconazole oral solution with fluconazole oral solution for primary prophylaxis of fungal infections in patients with haematological malignancy and profound neutropenia. *J Antimicrob Chemother* 2006; 57: 317–325.
78. Marr KA, Crippa F, Leisenring W *et al.* Itraconazole versus fluconazole for prevention of fungal infections in patients receiving allogeneic stem cell transplants. *Blood* 2004; 103: 1527–1533.
79. Wingard JR, Baden LR, Kurtzberg J *et al.* Response to: voriconazole prophylaxis and the risk of invasive fungal infection after allogeneic HCT. [eLetter]. http://bloodjournal.hematologylibrary.org/content/116/24/5111/reply#bloodjournal_el_1071 (accessed on 8 February 2012).
80. Girmenia C, Aversa F, Micozzi A *et al.* Voriconazole prophylaxis and the risk of invasive fungal infection after allogeneic HCT. [eLetter]. http://bloodjournal.hematologylibrary.org/content/116/24/5111/reply#bloodjournal_el_1071 (accessed on 8 February 2012).
81. Marks D, Kibbler C, Cook G *et al.* Voriconazole or itraconazole for antifungal prophylaxis in patients with grade II–IV acute or extensive chronic graft-versus-host disease. *Bone Marrow Transplant* 2010; 45: S78–S327, Abstract 1253.
82. Garcia-Vidal C, Upton A, Kirby KA, Marr KA. Epidemiology of invasive mold infections in allogeneic stem cell transplant recipients: biological risk factors for infection according to time after transplantation. *Clin Infect Dis* 2008; 47: 1041–1050.
83. Chabrol A, Cuzin L, Huguet F *et al.* Prophylaxis of invasive aspergillosis with voriconazole or caspofungin during building work in patients with acute leukemia. *Haematologica* 2010; 95: 996–1003.
84. Gergis U, Markey K, Greene J *et al.* Voriconazole provides effective prophylaxis for invasive fungal infection in patients receiving glucocorticoid therapy for GVHD. *Bone Marrow Transplant* 2010; 45: 662–667.

85. Martin T, Sharma M, Damon L *et al.* Voriconazole is safe and effective as prophylaxis for early and late fungal infections following allogeneic hematopoietic stem cell transplantation. *Transpl Infect Dis* 2010; 12: 45–50.
86. Siwek GT, Pfaller MA, Polgreen PM *et al.* Incidence of invasive aspergillosis among allogeneic hematopoietic stem cell transplant patients receiving voriconazole prophylaxis. *Diagn Microbiol Infect Dis* 2006; 55: 209–212.
87. Torres A, Serrano J, Rojas R *et al.* Voriconazole as primary antifungal prophylaxis in patients with neutropenia after hematopoietic stem cell transplantation or chemotherapy for acute myeloid leukemia. *Eur J Haematol* 2010; 84: 271–273.
88. Vehreschild JJ, Bohme A, Buchheidt D *et al.* A double-blind trial on prophylactic voriconazole (VRC) or placebo during induction chemotherapy for acute myelogenous leukaemia (AML). *J Infect* 2007; 55: 445–449.
89. Collins CD, Ellis JJ, Kaul DR. Comparative cost-effectiveness of posaconazole versus fluconazole or itraconazole prophylaxis in patients with prolonged neutropenia. *Am J Health Syst Pharm* 2008; 65: 2237–2243.
90. de la Camara R, Jarque I, Sanz MA *et al.* Economic evaluation of posaconazole vs fluconazole in the prevention of invasive fungal infections in patients with GVHD following haematopoietic SCT. *Bone Marrow Transplant* 2010; 45: 925–932.
91. de Vries R, Daenen S, Tolley K *et al.* Cost effectiveness of itraconazole in the prophylaxis of invasive fungal infections. *Pharmacoeconomics* 2008; 26: 75–90.
92. Stam WB, O'Sullivan AK, Rijnders B *et al.* Economic evaluation of posaconazole vs. standard azole prophylaxis in high risk neutropenic patients in the Netherlands. *Eur J Haematol* 2008; 81: 467–474.
93. Cordonnier C, Rovira M, Maertens J *et al.* Voriconazole for secondary prophylaxis of invasive fungal infections in allogeneic stem cell transplant recipients: results of the VOSIFI study. *Haematologica* 2010; 95: 1762–1768.
94. Fukuda T, Boeckh M, Guthrie KA *et al.* Invasive aspergillosis before allogeneic hematopoietic stem cell transplantation: 10-year experience at a single transplant center. *Biol Blood Marrow Transplant* 2004; 10: 494–503.
95. Martino R, Parody R, Fukuda T *et al.* Impact of the intensity of the pretransplantation conditioning regimen in patients with prior invasive aspergillosis undergoing allogeneic hematopoietic stem cell transplantation: a retrospective survey of the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. *Blood* 2006; 108: 2928–2936.
96. Offner F, Cordonnier C, Ljungman P *et al.* Impact of previous aspergillosis on the outcome of bone marrow transplantation. *Clin Infect Dis* 1998; 26: 1098–1103.
97. Cowie F, Meller ST, Cushing P, Pinkerton R. Chemoprophylaxis for pulmonary aspergillosis during intensive chemotherapy. *Arch Dis Child* 1994; 70: 136–138.
98. Cordonnier C, Maury S, Pautas C *et al.* Secondary antifungal prophylaxis with voriconazole to adhere to scheduled treatment in leukemic patients and stem cell transplant recipients. *Bone Marrow Transplant* 2004; 33: 943–948.
99. Masamoto Y, Nannya Y, Kurokawa M. Voriconazole is effective as secondary antifungal prophylaxis in leukemia patients with prior pulmonary fungal disease: case series and review of literature. *J Chemother* 2011; 23: 17–23.
100. Zhang P, Song A, Wang Z, Feng S, Qiu L, Han M. Hematopoietic SCT in patients with a history of invasive fungal infection. *Bone Marrow Transplant* 2009; 43: 533–537.
101. Dignan F, Grigoriadou V, Maxwell F *et al.*. Effective secondary antifungal prophylaxis with voriconazole. Presented at: European Hematology Association; June 12–15, 2008; Copenhagen, Denmark. Abstract 0183
102. de Fabritiis P, Spagnoli A, Di BP *et al.* Efficacy of caspofungin as secondary prophylaxis in patients undergoing allogeneic stem cell transplantation with prior pulmonary and/or systemic fungal infection. *Bone Marrow Transplant* 2007; 40: 245–249.
103. Kruger WH, Russmann B, de WM *et al.* Haemopoietic cell transplantation of patients with a history of deep or invasive fungal infection during prophylaxis with liposomal amphotericin B. *Acta Haematol* 2005; 113: 104–108.
104. Allinson K, Kolve H, Gumbinger HG, Vormoor HJ, Ehlert K, Groll AH. Secondary antifungal prophylaxis in paediatric allogeneic haematopoietic stem cell recipients. *J Antimicrob Chemother* 2008; 61: 734–742.
105. Pappas PG, Kauffman CA, Andes D *et al.* Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; 48: 503–535.
106. Marr KA, Bow E, Chiller T *et al.* Fungal infection prevention after hematopoietic cell transplantation. *Bone Marrow Transplant* 2009; 44: 483–487.
107. Tomblyn M, Chiller T, Einsele H *et al.* Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant* 2009; 15: 1143–1238.
108. Cornely OA, Bohme A, Buchheidt D *et al.* Primary prophylaxis of invasive fungal infections in patients with hematologic malignancies. Recommendations of the Infectious Diseases Working Party of the German Society for Haematology and Oncology. *Haematologica* 2009; 94: 113–122.
109. Ruping MJ, Heinz WJ, Kindo AJ *et al.* Forty-one recent cases of invasive zygomycosis from a global clinical registry. *J Antimicrob Chemother* 2010; 65: 296–302.